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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/996,771	12/24/92	WALLACE R	

CHAMBERS, S EXAMINER

18N2/0712

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ART UNIT	PAPER NUMBER
1807	

DATE MAILED: 07/12/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on Jan 28/93 (Jun 3/93) ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-47 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-47 are rejected.
5. ☒ Claims 10 ~~are~~ is objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

To aid in correlating any papers for this application, correspondence regarding this application should be directed to Group 180 Art Unit 1807.

Examiner notes that applicant's amendment before action adding claims 29-47 was not received by Group 180 until May 26, 1993, several days after the First Office Action on the case. Nevertheless, because the amendment was received at the PTO prior to the mailing of the First Office Action examiner is issuing this Supplemental Office Action and restarting the time period.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide a written descriptive basis. Applicant's newly submitted claims contain material which examiner has been unable to find in the original specification. MPEP 714.03 indicates that applicants should specifically point out the support for any amendments. See also 706.03(n). Applicant is requested to point out with particularity to exactly where the following material is found in the specification as filed. (1) enzyme tag, e.g., see claim 31; (2) fluorescent tag, e.g., see claim 31; (3) colorimetric tag, e.g., see claim 31; (4) immobilized linked probe product, e.g., see claim 32; (5) immobilized by a covalent bond, e.g., see claim 33; (6) immobilized by an affinity bond, e.g., see claim 33; (7) immobilizing the test substance, e.g., see claim 34; (8) immobilizing the non-label probe before step (e), e.g., see claim 35; (9) ligation with an agent other than a ligase, which is required by the doctrine of claim differentiation by the dependency of claim 37, because all of the claims save number 37 incorporate the use of agents other than a ligase, this rejection would apply to all claims except number 37; (10) migration at "substantially different rates than said linked probe product", e.g., see claim 38; (11) labeling with different labels in the same assay, e.g.,

see claim 39; (12) a generic assay in which "said end region of said target probe consists of the end nucleotide of said target probe and the three nucleotides adjacent to it, e.g., see claim 44; and (13) a generic assay in which "said end region of said target probe consists of the end nucleotide of said target probe and the nucleotide adjacent to it, e.g., see claim 45.

Claims 29-36 and 38-47 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-28 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 calls for "wherein oligonucleotides of any of said pairs of oligonucleotides comprising the 3' end of [the] ligation product are phosphorylated at their 5' ends." This is either confusing, in which case claim 18 is rejected for being confusing, or claims 1-17 and 19-28 are not enabled in light of the doctrine of claim differentiation. It is well known and a matter of common knowledge that ligases need a 5' phosphorylation. See Maniatis et al., page 146 and 147. Thus, the oligonucleotide which forms the 3' end will have to be phosphorylated in order to get the reaction to work. The doctrine of claim differentiation precludes the reading of these claim limitations into the independent claim. See Laitram Corp. v. Cambridge Wire Cloth Co., 9 USPQ2d 1289 (Fed. Cir. 1988). Therefore, there must be some other method for obtaining ligation other than having a 5' phosphorylation. Examiner is not aware of any method to obtain ligation without phosphorylation and applicants have not provided any teaching. It would require undue experimentation by one of ordinary skill in the art to determine how to ligate without the phosphorylation. Furthermore, the use of the phrase "oligonucleotides of said pairs" refers to the oligonucleotide before the ligation but applicant refers to "ultimate ligation product" which is after the ligation. Applicant is requested to clarify this matter.

Claims 1-4, 10, and 29-47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 have a preamble indicating that they are a method for distinguishing between variants; unfortunately, there is no detection step in the claimed invention. It is not clear how one would distinguish without any detection step. In Ex parte Erlich, 3 USPQ2d 1010 (1987) the Board of Appeals indicated that "a method claim should at least recite positive active step(s) so that the claim will 'set out and circumscribe a particular area with a reasonable degree of precision and particularity'" to avoid running afoul of 35 USC 112 second paragraph. In the instant case, applicant requires distinguishing but there is no distinguishing step: this is confusing.

Claim 10 indicates that the target sequence is a single nucleotide: this is confusing and makes the use of the term "target sequence" vague and indefinite in all of the other claims: how can a sequence be one base? Applicant's specification indicates that substrate sequences "are oligonucleotide sequences complementary to sequences which immediately flank each side of a variant nucleotide in a target sequence"; thus, it is clear from the specification that the variant nucleotide is not itself a target sequence but is only part of a target sequence. Since hybridization to a single nucleotide is not known in this art, it must be that applicant means something else by this claim. Thus, the claim is confusing. This point was upheld at the Board on the parent case.

Claims 29-47 are a photocopy of a U.S. patent. The words are difficult to read and in some cases obliterated in the copy received by examiner. For example, the word "assay" in claims 29 and 32. Thus it is confusing. In addition, while applicant renumbered the photocopied claims of the U.S. patent, there was no change in the dependencies of the claims; therefore, the claims presently depend upon applicant's original claims. For example, claim 30 depends upon claim 1; presumably, claim 29 dependance was intended. This is confusing; but more importantly, it leads to a lack of antecedent basis in all of the claims. For example, claim 30 calls for "said target probe", "said adjacent probe", "said detecting", and "said label": non of which has

antecedent basis in applicant's claim 1. Applicant is requested to correct the dependencies of claims 30-47.

Claim 10 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from a multiply dependent claim. See MPEP 608.01(n). Although the MPEP recommends that such a claim not been further treated on the merits, examiner has made several rejections based on the claim in the interest of expediting prosecution of the case. Nevertheless, applicant is requested to correct the problem in the response to this Office Action.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action: "A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1, 2, 3, 4, 10, 29, and 30 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Wallace (E.P. 0 336 731). Wallace discloses a method of distinguishing a point mutation. See Table 1, Example 1. a point mutation is a specific species of "single nucleotide variant", i.e., a single nucleotide

which causes a mutation. Thus, the species is within the claimed genus. Pages 5 and 6 of Wallace describe a method for distinguishing a point mutation from the normal allele and use substrate sequences which are 8 and 14 nucleotides in length. Both of these sizes are within the claimed genus of 8 to 25 nucleotides. Wallace uses a reaction containing 200 mM NaCl (see page 6, line 63-64) and actually claims a reaction mixture comprising at least 200 mM NaCl (see claim 29): 200mM is within the range of 200 -500 mM. Wallace teaches the use of T4 DNA ligase and E.coli DNA ligase. See claim 12. Wallace teaches probing for a mutant allele which differs from the normal allele by a single nucleotide, which may be what applicant attempts to claim in Claim 10.

As set forth in In re van Langenhoven, 173 U.S.P.Q. 426 (C.C.P.A. 1972), to be entitled to filing date of previously filed application, application must satisfy requirements of 35 U.S.C. 120, among which is requirement that subject matter now claimed be disclosed in a manner prescribed by first paragraph of section 112 in prior application; since, to conform to section 112, claimed subject matter must be described in specification relied upon, subject matter which is first disclosed in continuation -in-part application is not entitled to filing date of parent application. The court stated that "the fact that some of the elements of the . . . claims have the support of the parent . . . applications does not change the result. As to given claimed subject matter, only one effective date is applicable. Whether or not the requirements of section 120 are satisfied is determinative of that date." Id. at 429, emphasis by examiner. Thus, when applicants attempt to enlarge the scope of their invention, they run the risk of having their own art used against them. Examiner has been unable to find support in the original parent application for the following concepts: (1) nucleotide variants, although support for "point mutations" is present; (2) "head to tail juxtaposition"; (3) "conditions effective to ligate said substrate sequences but only in the absence of a mismatch"; (4) a range of "8-25 nucleotides in length"; (5) a range of sodium chloride "concentration of 200 mM to 500 mM"; (6) a range of spermidine "concentration of 2 to 5 mM"; (7) "thermophilus ligase"; and (8) a target sequence of a single nucleotide. In addition, it appears that (9) there is no method of obtaining thermophilus ligase provided in the parent application, thus, even if the ligase were

mentioned it would not satisfy the requirements of 35 U.S.C. 120. If applicant will point out with particularity to exactly where teachings of (1) - (9) are found in the original parent application it would greatly simplify prosecution of the instant case.

Claims 1, 2, 3, 4, 10, 29, and 30 are rejected under 35 U.S.C. 103 as being unpatentable over Backman et al. (E.P. 0 320 308) taken with Wallace (E.P. 0 336 731) in view of Sambrook et al. and Hames et al. Both Backman et al. and Wallace teach the ligase chain reaction (LCR). Backman et al. teach the LCR can be used to detect the presence of specific sequence. Nucleotide variants have a different sequence; thus, one of ordinary skill in the art would immediately envisage that the Backman method could be used to determine the presence or absence of sequence. Such is taught by Wallace. See Table 1, Example 1. a point mutation is a specific species of "single nucleotide variant", i.e., a single nucleotide which causes a mutation. Backman et al. teach using oligonucleotides of 10-200 bases (see page 3, column 1, lines 59-60), and actually use oligonucleotides of 25, 21, 18, and 14 nucleotides which is well within the claimed range of applicant. Backman et al.do not limit the invention to any particular salt range; however, one of ordinary skill in the art would realize that hybridization is favored by increased ionic strength as taught by Hames et al. Furthermore, Wallace specifically uses a reaction containing 200 mM NaCl (see page 6, line 63-64) and actually claims a reaction mixture comprising at least 200 mM NaCl (see claim 29): 200mM is within the range of 200 -500 mM and one of ordinary skill would increase this concentration in order to achieve the benefits promised by Hames et al. Backman et al. specifically suggest using a thermostable ligase such as that from Thermus thermophilus and describe the general method to purify such a ligase. See page 3, column 2, lines 19-22. Backman et al. describe the method and indicate that conditions should be adjusted so that the ligase "will not ligate blunt ends of DNA in the sample." Although Backman et al. do not describe specific methods to use to avoid blunt end ligation, the ligation of blunt ends is well known and a matter of common knowledge. Such is taught in **Molecular Cloning** by Sambrook et al. where it is taught that blunt end ligation is favored by the absence of polyamines such as spermidine. one of ordinary skill in the art, attempting to avoid blunt end ligation would have avoided the "absence of

polyamines such as spermidine" and would have included several mM spermidine in the reaction mixture. Thus applicant's invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

As set forth in In re van Langenhoven, 173 U.S.P.Q. 426 (C.C.P.A. 1972), to be entitled to filing date of previously filed application, application must satisfy requirements of 35 U.S.C. 120, among which is requirement that subject matter now claimed be disclosed in a manner prescribed by first paragraph of section 112 in prior application; since, to conform to section 112, claimed subject matter must be described in specification relied upon, subject matter which is first disclosed in continuation -in-part application is not entitled to filing date of parent application. The court stated that "the fact that some of the elements of the . . . claims have the support of the parent . . . applications does not change the result. As to given claimed subject matter, only one effective date is applicable. Whether or not the requirements of section 120 are satisfied is determinative of that date." Id. at 429, emphasis by examiner. Examiner has been unable to find support in the original parent application for the following concepts: (1) nucleotide variants, although support for "point mutations" is present; (2) "head to tail juxtaposition"; (3) "conditions effective to ligate said substrate sequences but only in the absence of a mismatch"; (4) a range of "8-25 nucleotides in length"; (5) a range of sodium chloride "concentration of 200 mM to 500 mM"; (6) a range of spermidine "concentration of 2 to 5 mM"; (7) "thermophilus ligase"; (8) a target sequence of a single nucleotide. In addition, it appears that (9) there is no method of obtaining thermophilus ligase provided in the parent application, thus, even if the ligase were mentioned it would not satisfy the requirements of 35 U.S.C. 120. If applicant will point out with particularity to exactly where teachings of (1) - (9) are found in the original parent application it would greatly simplify prosecution of the instant case.

Claims 12, 16, 17, 18, 19, 29, and 30 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Whiteley et al. See claims 6-8 and 21-22. Although it is well known and a matter of common knowledge that

increasing the temperature or the stringency will denature the duplex, such is also taught by Whiteley et al. See page 6, lines 21-25.

Claims 1-47 are rejected under 35 U.S.C. 103 as being unpatentable over Mullis et al. taken with Carr and Whiteley et al. in view of Hames et al. and Sambrook et al. Mullis et al. teach a method of amplifying a contiguous fragment of nucleic acid. This method entails utilizing as initial templates two single stranded complementary nucleic acid sequences each including a target sequence. Mullis et al. teach that when the sample is RNA, then reverse transcriptase can be used to make a DNA copy in order to more effectively use the method. Primers are then hybridized to each of the two templates. In Mullis et al. the rest of the strand is made by adding one oligonucleotide at a time through the use of a method called primer extension. After the new single strands are made both of the (now) double stranded nucleic acids are denatured to produce four separate strands: two of the four are the initial template strands and the other two of the four are the newly made strands. This process is iterated, but it should be noted that this time there are four template strands: the two initial ones and the two newly made ones. The reaction is repeated as often as desired to produce a geometric expansion of the number of strands (i.e. exponential amplification). Mullis et al. calls for a primer for each of the two strands, with the addition of only a single primer there would not be an exponential increase in the number of strands. This is because at the end of the first cycle there would only be a single template strand even though there would be two strands that were the complement. Thus repetition of the procedure with only a single primer would only produce a linear or arithmetic increase in the number of strands. This result is apparent from an inspection of Fig. 4-1 through 4-3 of Mullis et al. in which a primer for both strands is used and a comparison of what would be the result if only one strand were used. Indeed, it is well known that extension of a single strand will result in both the original copy (it was never affected by polymerization) and a new strand (see CYCLES 1 and 2 of Fig. 4-1 through 4-3). However, Mullis et al. were most concerned with the exponential increase and its concomitant increase in sensitivity of detection. As indicated, the cycling process occurs one or more times and Mullis et al. point out the great value of repeating the process a large number of times since it results in a geometric amplification of the

duplex. Mullis et al. forms the complementary strand using a polymerase enzyme while applicants form the complementary strand by ligating fragments together; however, one of ordinary skill in the art would know that a complementary strand could be formed by ligating smaller fragments together. Carr and Whiteley et al. teach that a complementary strand can be formed by ligating fragments together either with a ligase (Carr and Whiteley et al.) or by use of a polymerase (Carr). They also teach that their method can be used "for discriminating a specific base sequence from a variant base sequence". See, e.g., Carr abstract, Whiteley et al. at page 2, lines 1 et seq., where they describe that their method is an improvement to the old method fro detecting the sickle cell mutation, see also page 8, lines 20-25. Both Carr and Whiteley et al. suggest using a 15-mer in their method (page 9, lines 9-10 of Carr and page 16, lines 13-15 of Whiteley et al.). Both Carr and Whiteley et al. teach the use of radioisotopes: Carr, page 6, lines 41-42, Whiteley et al. page 10, lines 25-34. One of ordinary skill in the art would know that what was important was the formation of the complementary sequence and that whether one used short fragments of DNA and a polymerase or short fragments of DNA and a ligase with or without a polymerase that the only thing of importance was the formation of a complementary strand which could be used in subsequent reactions. In regards to claim 15 in which a complement is only formed for one of the two strands it would have been obvious to copy only one of the two strands if one wished to forego the benefits of an exponential increase or only had a primer for one of the strands. Thus the invention as claimed would have been obvious to one of ordinary skill in the art at the time the invention was made. Hames et al. is provided simply as a teaching that one of ordinary skill in the art would be motivated to use higher concentrations of NaCl in order to perfect the reaction. Sambrook et al. is provided to show that one of ordinary skill in the art would have added polyamines and dephosphorylated the 5' end of the 5' oligonucleotide used to form the ligation product. Thus applicants invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

Claims 1-47 are rejected under 35 U.S.C. 103 as being unpatentable over Carr and Whiteley et al. taken with Mullis et al. in view of Hames et al. and Sambrook et al. Carr and Whiteley et al. teach an assay method which

entails: utilizing as an initial template and hybridizing two fragments to it. Ligating those fragments together and denaturing the fragments. They do not iterate the process to obtain an amplification and they do not use both strands of the initial template. They also teach that their method can be used "for discriminating a specific base sequence from a variant base sequence". See, e.g., Carr abstract, Whiteley et al. at page 2, lines 1 et seq., where they describe that their method is an improvement to the old method fro detecting the sickle cell mutation, see also page 8, lines 20-25. Both Carr and Whiteley et al. suggest using a 15-mer in their method (page 9, lines 9-10 of Carr and page 16, lines 13-15 of Whiteley et al.). Both Carr and Whiteley et al. teach the use of radioisotopes: Carr, page 6, lines 41-42, Whiteley et al. page 10, lines 25-34. The probes of applicant are simply probes which cross the mutation pointed out by Whiteley et al. See page 2. Mullis et al. teach the importance and value of using both strands in a process of making copies of nucleic acid, and teach an iterative procedure in order to amplify the target sequence. Mullis et al. teach that when the sample is RNA, then reverse transcriptase can be used to make a DNA copy in order to more effectively use the method. The only difference between applicant's method and that of Carr and Whiteley et al. is that applicant uses both strands (primary references use only one strand) and iterates the procedure to amplify the product. This is exactly what Mullis et al. teach is of great importance for increasing the signal strength of an assay. The method of modification to the primary references (i.e. use both strands instead of only one and to do the reaction more than once) to obtain an amplification would be obvious in light of the teachings of Mullis et al. and one would be motivated to do this to obtain the great increase in signal strength obtained from an amplification of the sequence to be detected. In regards to claim 15 in which a complement is only formed for one of the two strands it would have been obvious to copy only one of the two strands if one wished to forego the benefits of an exponential increase or only had a primer for one of the strands. Thus the invention as claimed would have been obvious to one of ordinary skill in the art at the time the invention was made. Hames et al. is provided simply as a teaching that one of ordinary skill in the art would be motivated to use higher concentrations of NaCl in order to perfect the reaction. Sambrook et al. is provided to show that one of ordinary skill in the art would have added polyamines and

dephosphorylated the 5' end of the 5' oligonucleotide used to form the ligation product. Thus applicants invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

No claim is allowed.

An inquiry concerning this communication should be directed to Scott A. Chambers, Ph.D. at telephone number 703-308-3885.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014.

Scott A. Chambers
Patent Examiner
Art Unit 1807

APPROVED
OCT 02 1993
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